

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/087126 A2(51) International Patent Classification⁷:

C07K

(74) Agents: STEFFE, Eric, K.; Sterne, Kessler, Goldstein & Fox P.L.L.C., 1100 New York Avenue, N.W., Washington, D.C. 20005-3934 et al. (US).

(21) International Application Number: PCT/US03/10571

(22) International Filing Date: 7 April 2003 (07.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

10/116,118 5 April 2002 (05.04.2002) US
60/413,471 26 September 2002 (26.09.2002) US

(71) Applicant (for all designated States except US): EPIMUNE INC. [US/US]; 5820 Nancy Ridge Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ISHIOKA, Glenn [US/US]; 11516 Hadar Drive, San Diego, CA 92126 (US). FIKES, John [US/US]; 4671 Robbins Street, San Diego, CA 92122 (US). TANGRI, Shabnam [IN/US]; 5683 Glenstone Way, San Diego, CA 92121 (US). SETTE, Alessandro [IT/US]; 5551 Linda Rosa Avenue, La Jolla, CA 92037 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCLITIC ANALOGS AND RELATED METHODS

(57) Abstract: Heteroclitic analogs of class I epitopes are prepared by providing conservative, semi-conservative, or non-conservative amino acid substitutions at positions 3 and/or 4 and/or 5 and/or 6 and/or 7 and/or 8 and/or 9 and/or 10 of these epitopes. The analogs are useful in eliciting immune responses with respect to the corresponding wild-type epitopes.

WO 03/087126 A2

BEST AVAILABLE COPY

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10571

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/53; A61K 38/00, 38/04, 39/00; C07H 21/04

US CL : 424/93.7, 185.1, 192.1; 435/7.1; 514/15; 530/328; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.7, 185.1, 192.1; 435/7.1; 514/15; 530/328; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
STIC searched SEQ ID NO: 2, 3, 5, 6, 8, 9, 11, 12-18 and 21-25 against protein databases

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/36452A2 (EPIMMUNE, INC. [US/US]) 25 MAY 2001 (25.05.2001), see entire document.	1-16, 34, 38-42, 44-46 and 48-63(in part)
Y	DYALL ET AL. Heteroclitic Immunization Induces Tumor Immunity. J. Exp. Med. 2 November 1998, Vol. 188, No. 9, pages 1553-1561, see entire article.	1-16, 34, 38-42, 44-46 and 48-63(in part)

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

Special categories of cited documents:	
* "A" document defining the general state of the art which is not considered to be of particular relevance	* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "B" earlier application or patent published on or after the international filing date	* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "O" document referring to an oral disclosure, use, exhibition or other means	* "&" document member of the same patent family
* "P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

23 April 2004 (23.04.2004)

Date of mailing of the international search report

23 AUG 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 872-9306

Authorized officer

Valerie Bed-Harris for
Marlene D. Harris, Ph.D.

Telephone No. 571-272-1600

BEST AVAILABLE COPY

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/10571

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 17-33, 35-37, 43, 47, 46(in part), 48-63(in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/10571

Continuation of Box I Reason 2:

Claims 17-33 were not searched because "composition" recited in the claims lack antecedent basis in the base claims. Claims 35-37 were not searched because "nucleic acid molecule" recited in the instant claims lack antecedent basis in the base claims. Claims 43 and 47 not searched because they are unclear in sections b and c in both claims and a non-sequential three part range is recited in part a of claim 47. Claim 46 was searched in part, exclusive of the analogs in Table 8 because no seq id no are disclosed in Table 8. Claims 48-63 were not searched in part as they pertain to the unclear non-searched portions of the base claims upon which they depend.

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.2, STN (EMBASE, BIOSIS, MEDLINE, CAPLUS, SCISEARCH)

search terms: Inventors' names, heteroclitic, peptide/s, class I MHC, motif, epitope/s

1/24

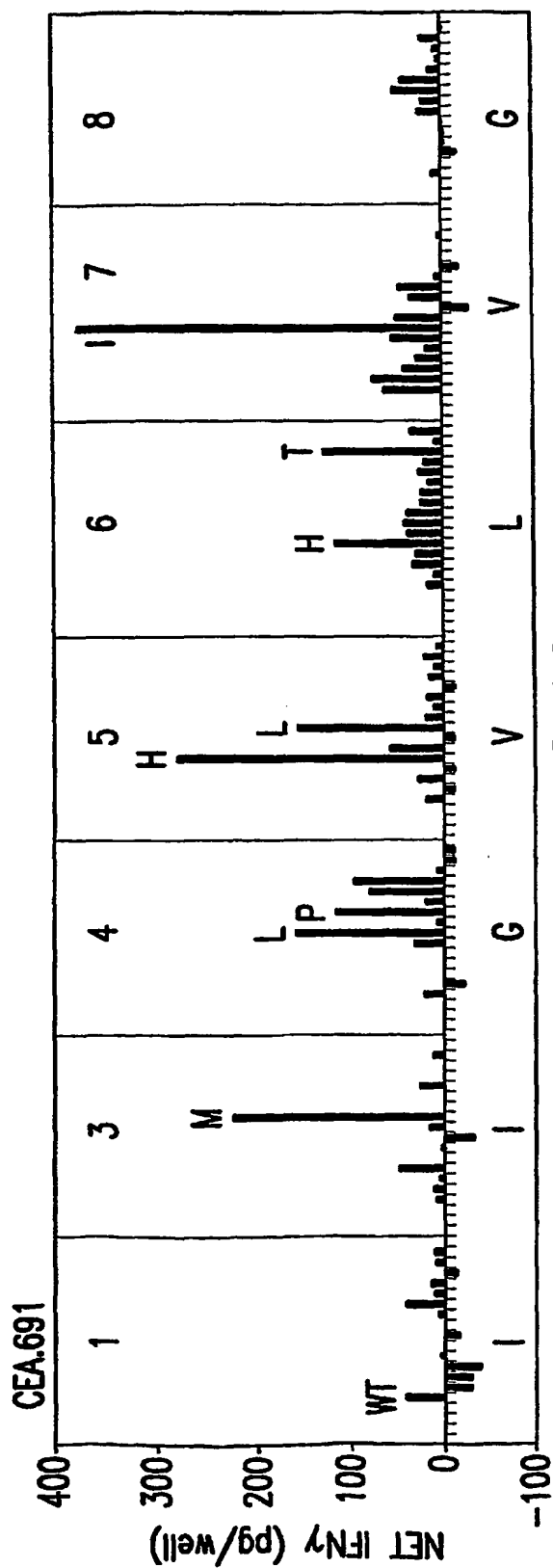


FIG.1A

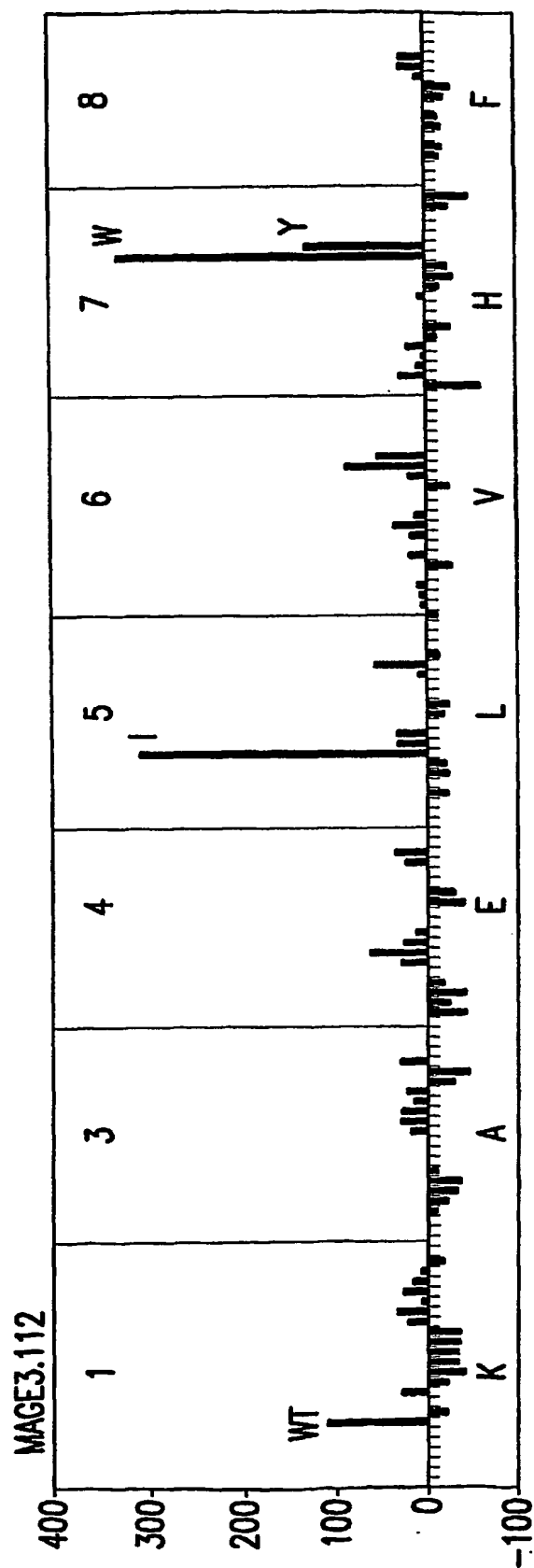
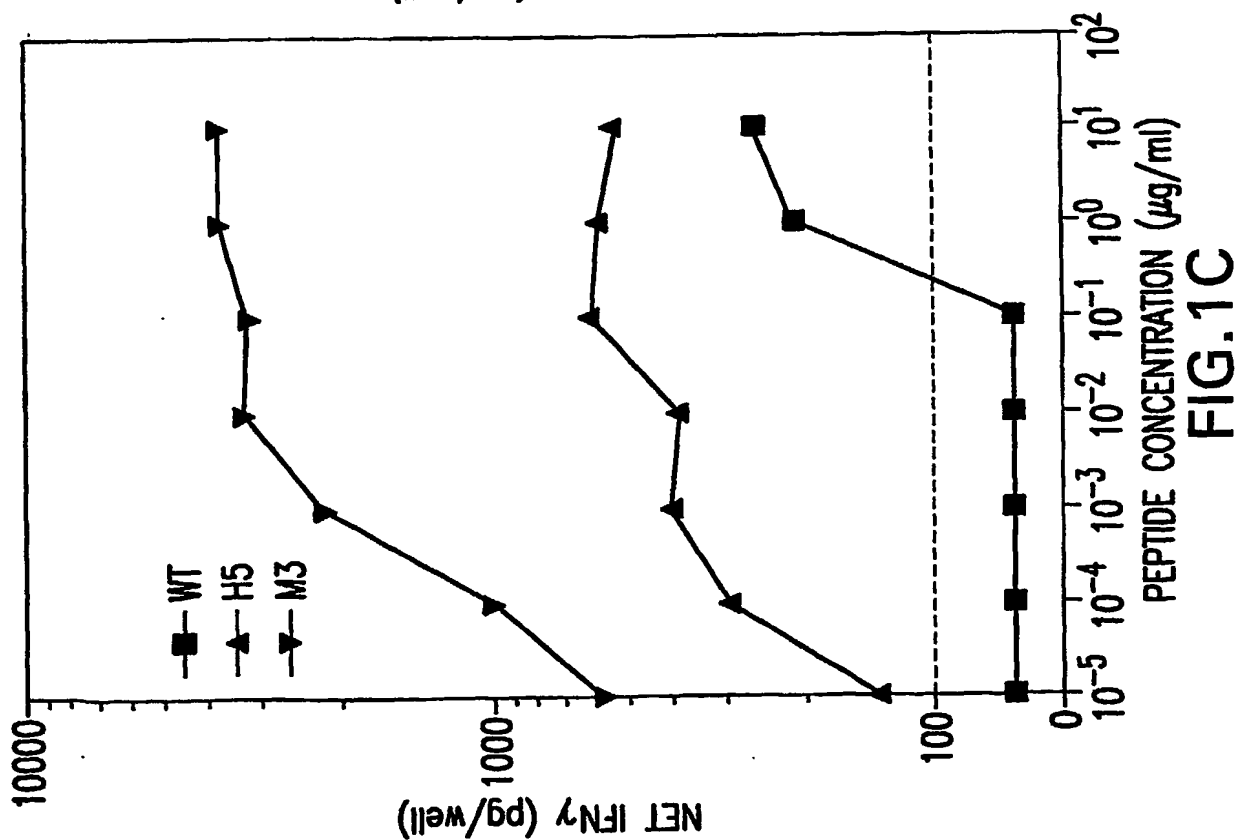
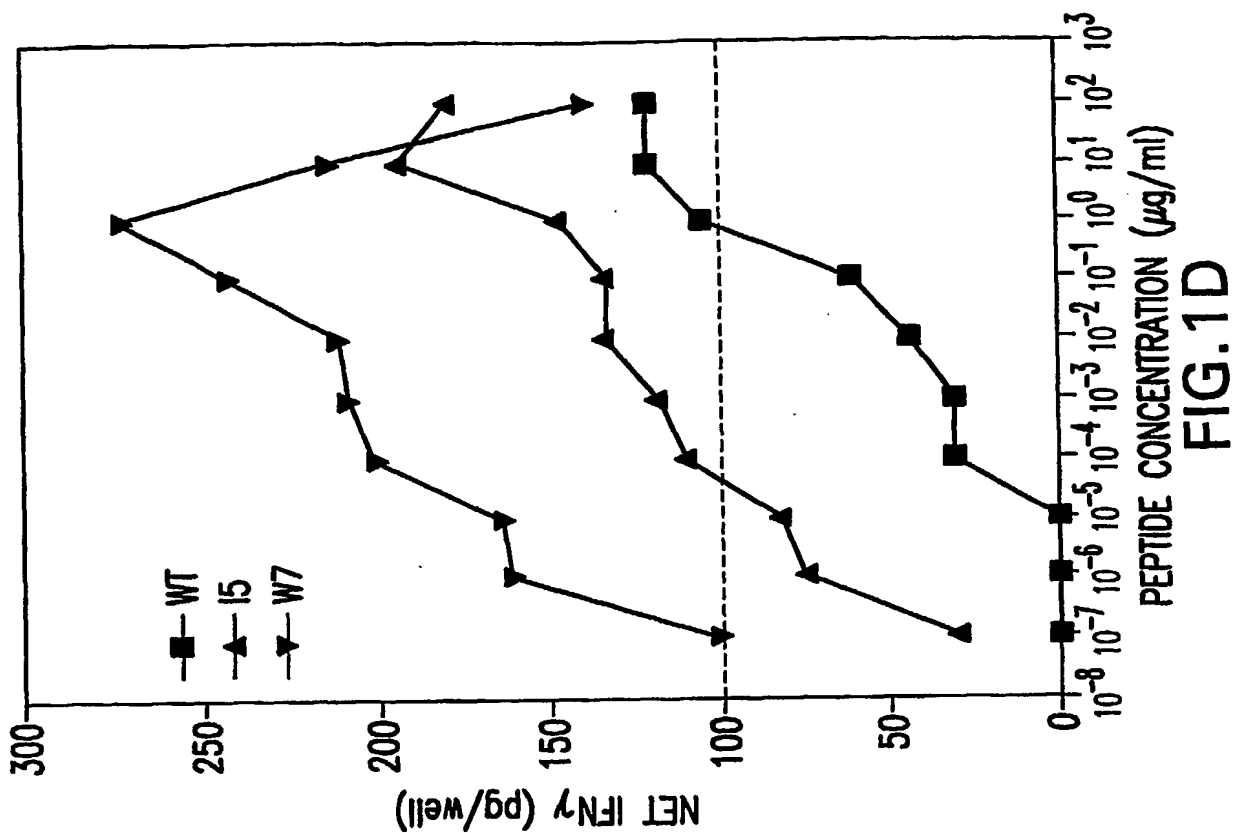


FIG.1B

2/24



3/24

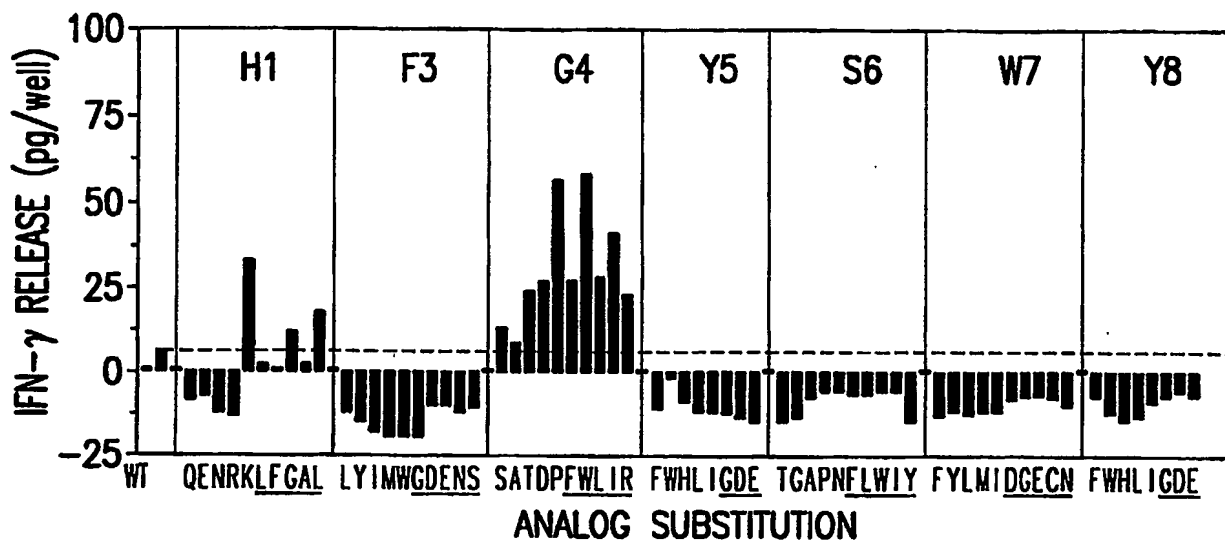


FIG.2A

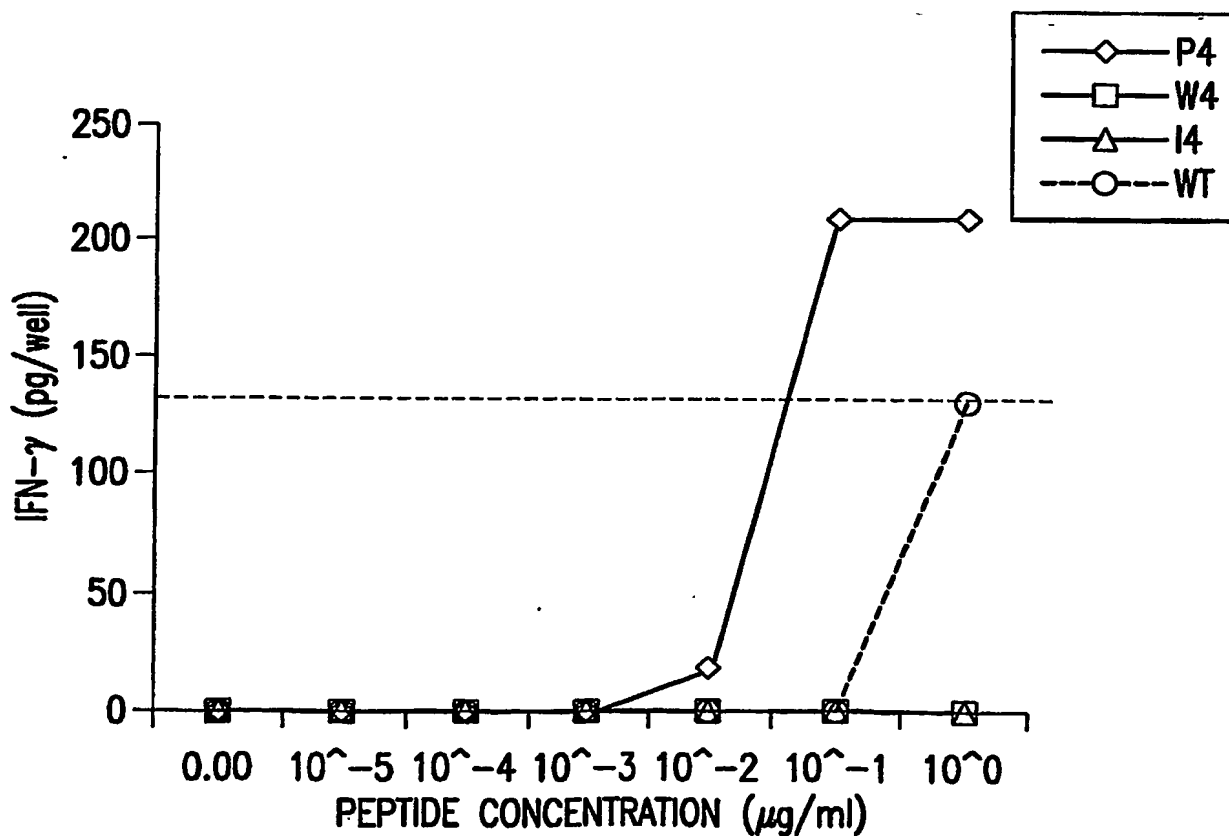


FIG.2B

4/24

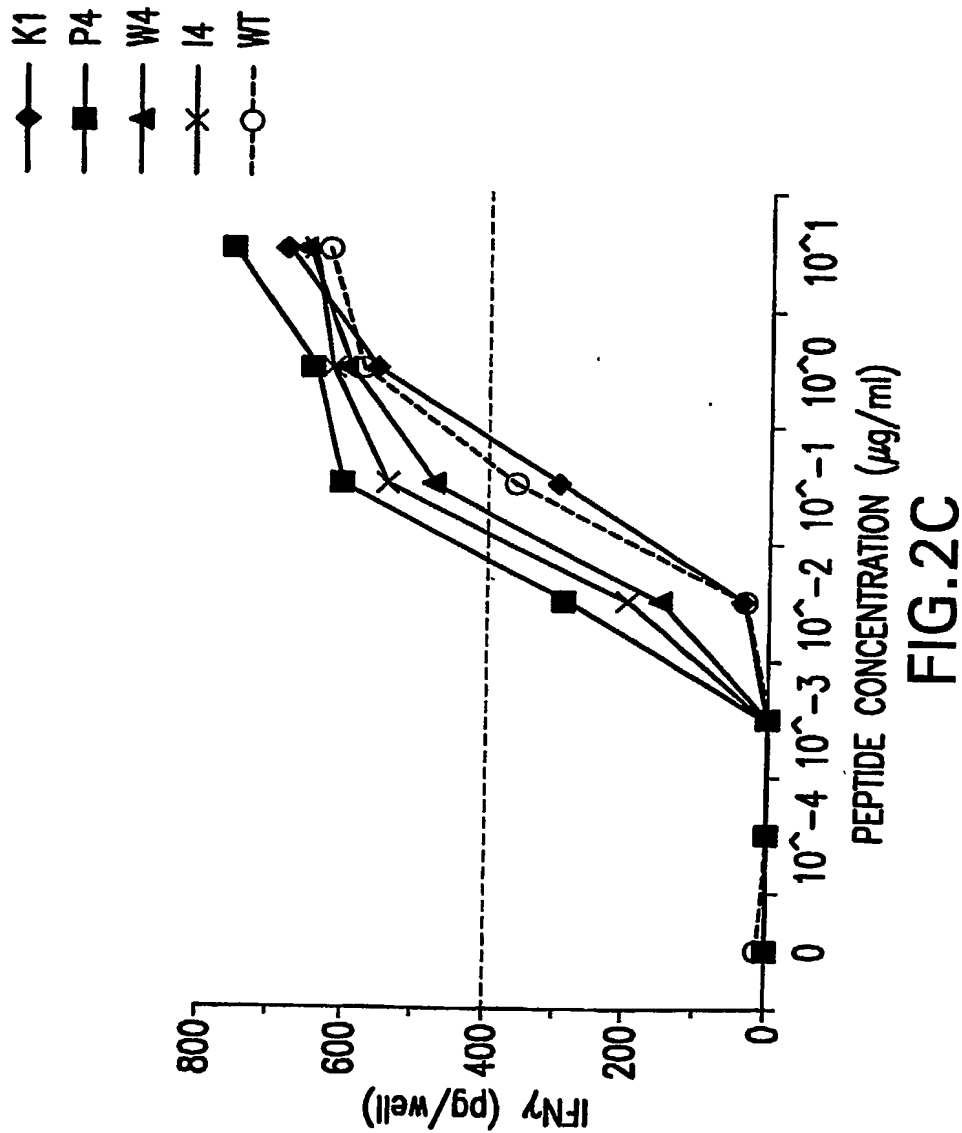


FIG.2C

5/24

IDENTIFICATION OF HETEROCLITIC ANALOGS OF THE CEA.61
EPIOTOPE FROM A CTL LINE GENERATED FROM DONOR xBB15.

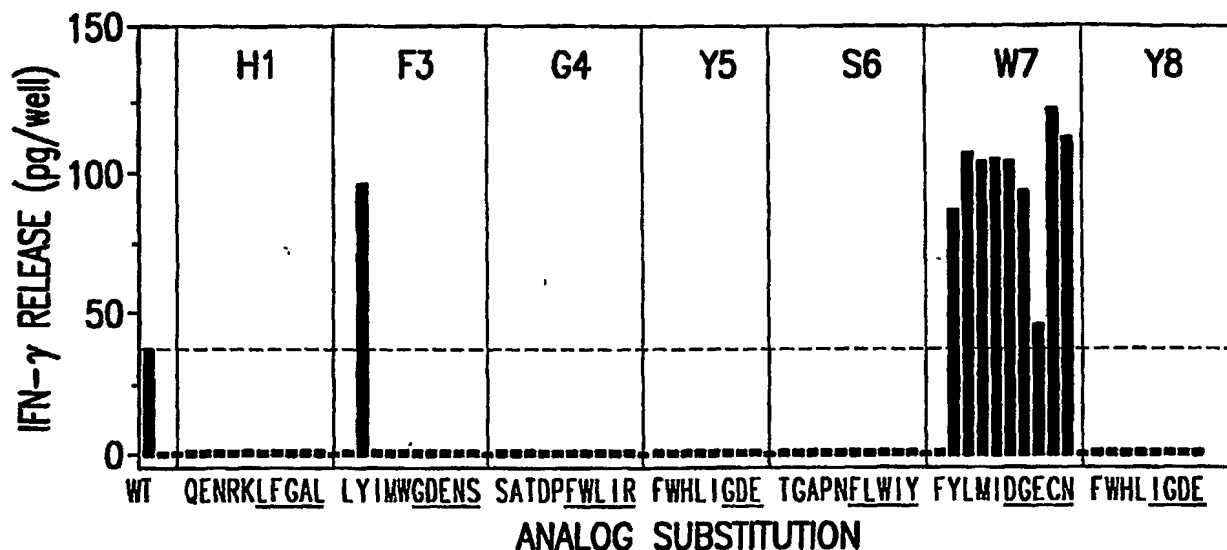


FIG.3A

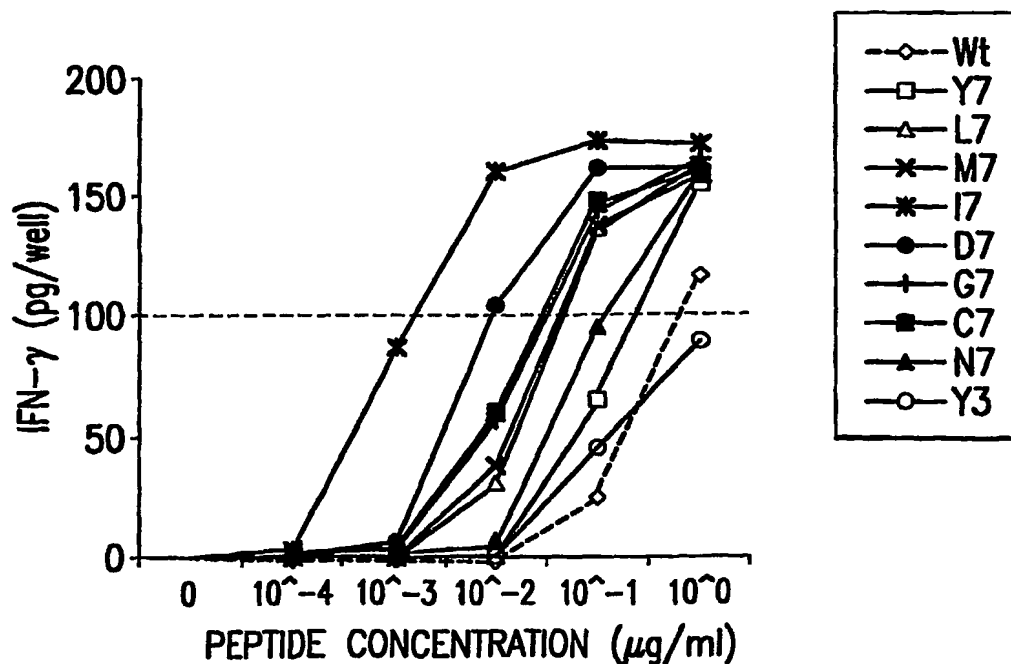


FIG.3B

6/24

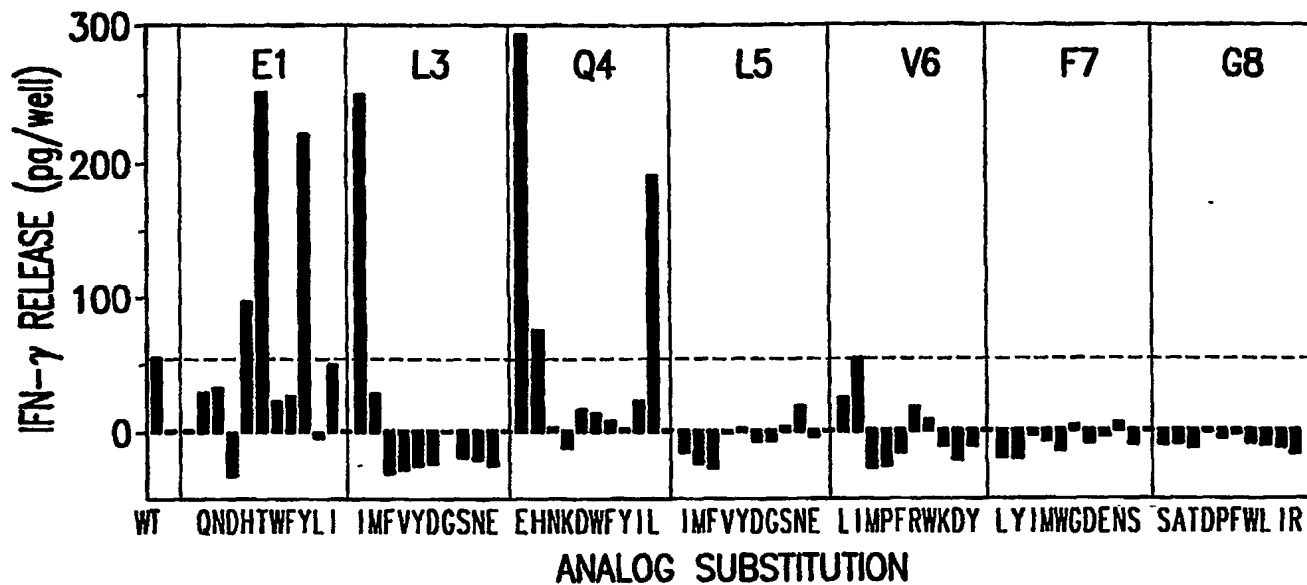
IDENTIFICATION OF HETEROCLITIC ANALOGS OF THE MAGE2.156
EPIOTOPE FROM A CTL LINE GENERATED FROM DONOR x662.

FIG.4A

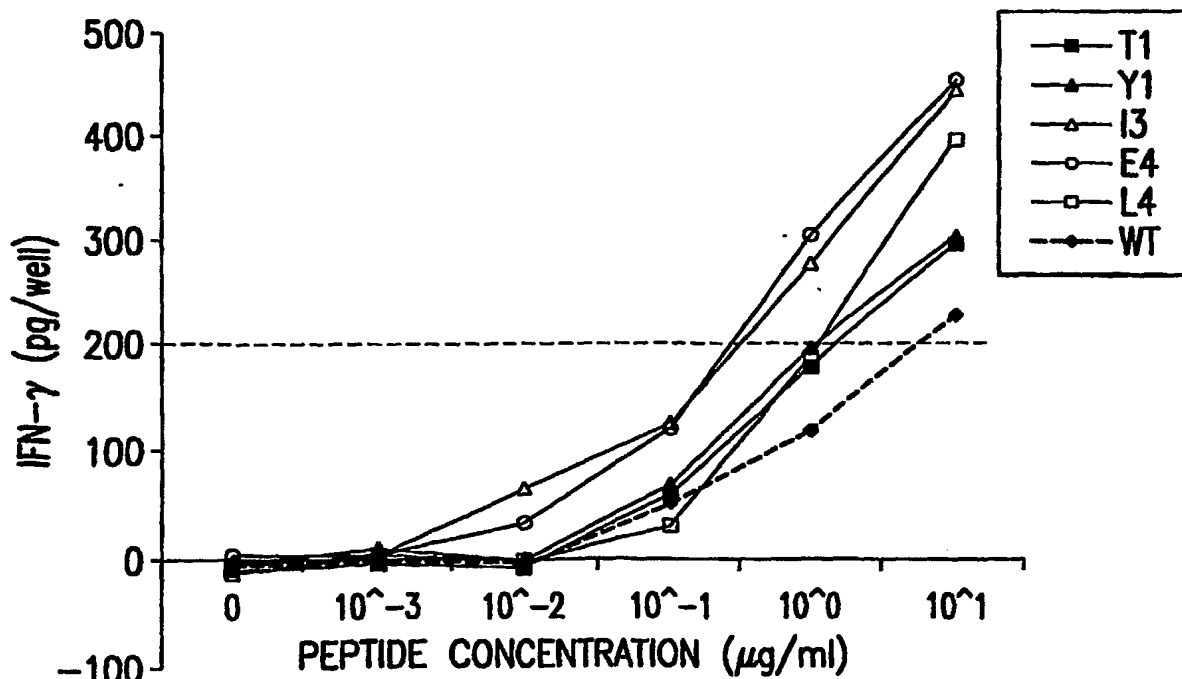


FIG.4B

7/24

IDENTIFICATION OF HETEROCLITIC ANALOGS OF THE MAGE2.156
EPIOTOPE FROM A CTL LINE GENERATED FROM DONOR x246.

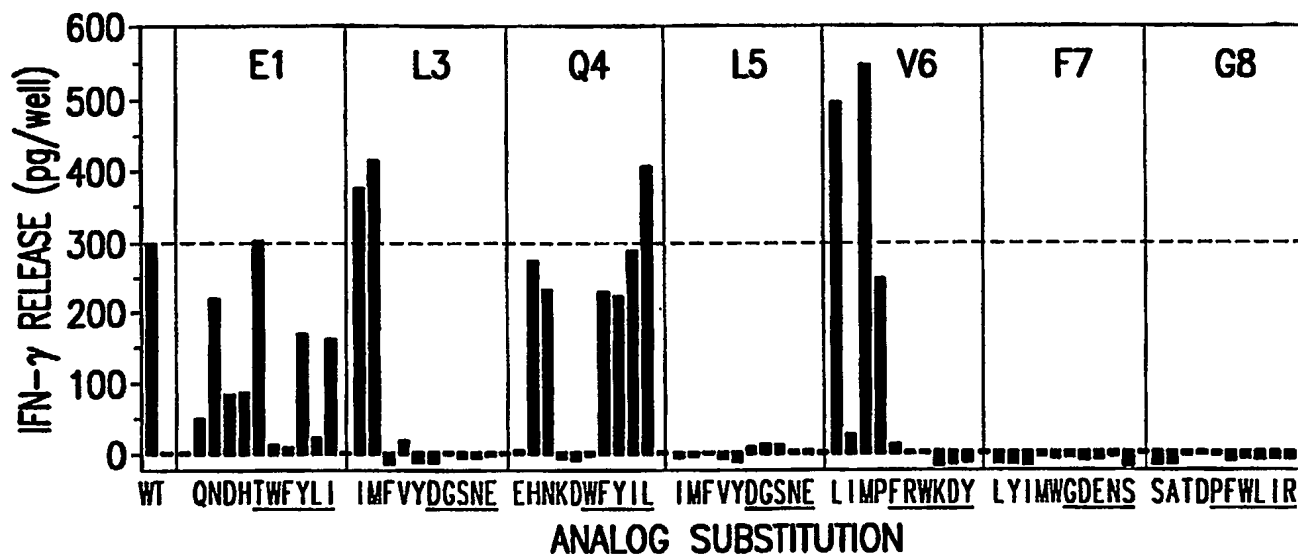


FIG.5A

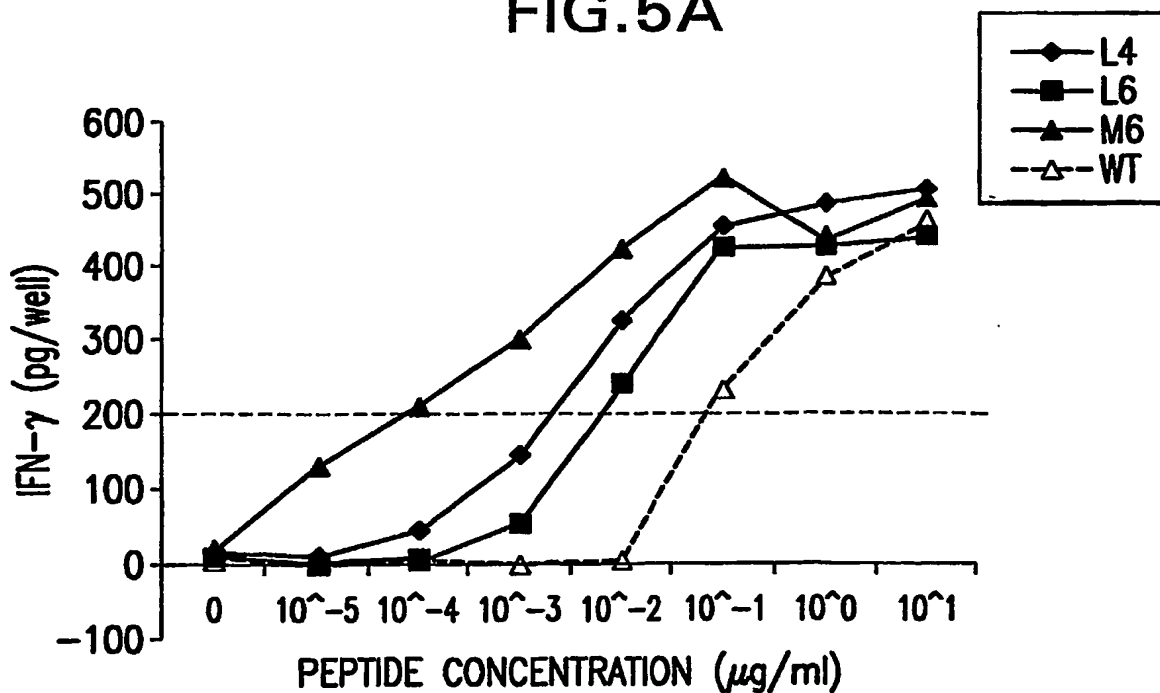


FIG.5B

8/24

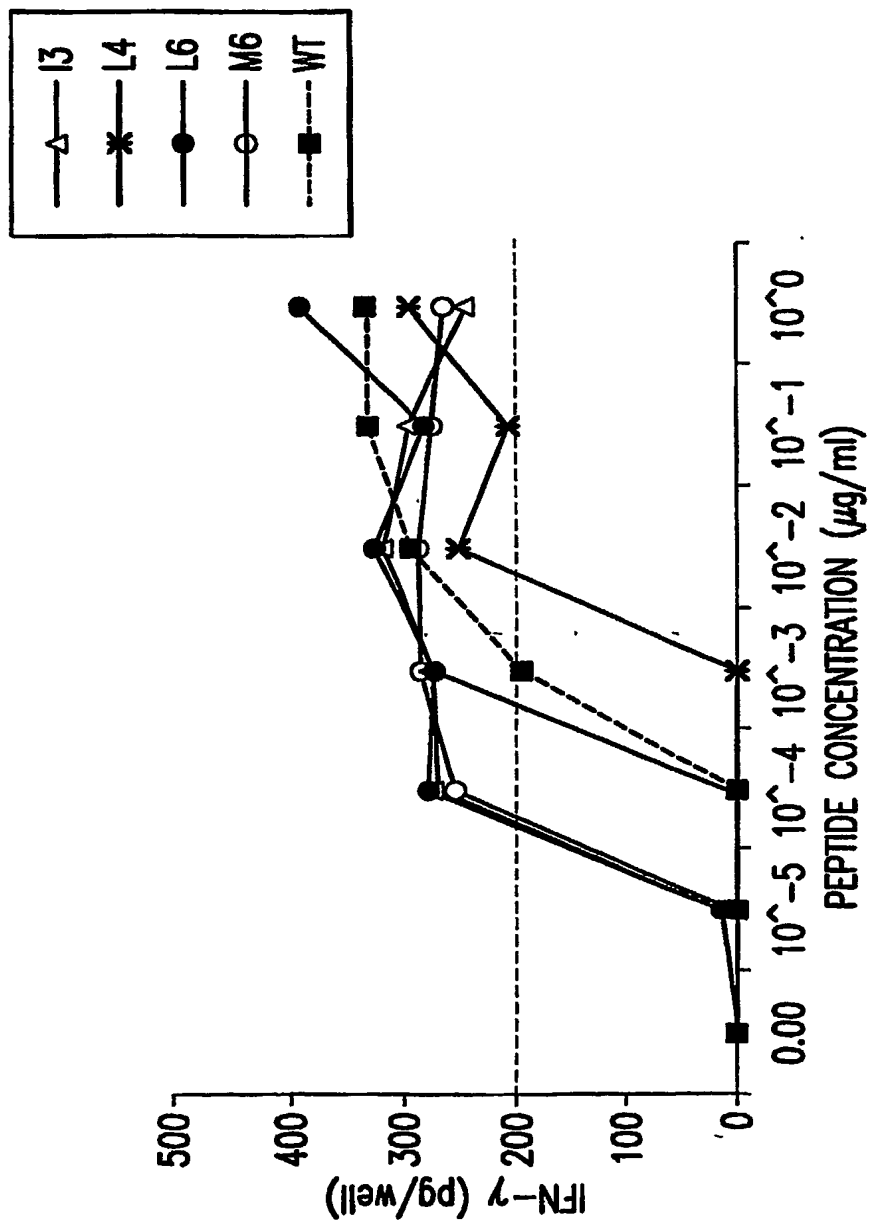


FIG.5C

9/24

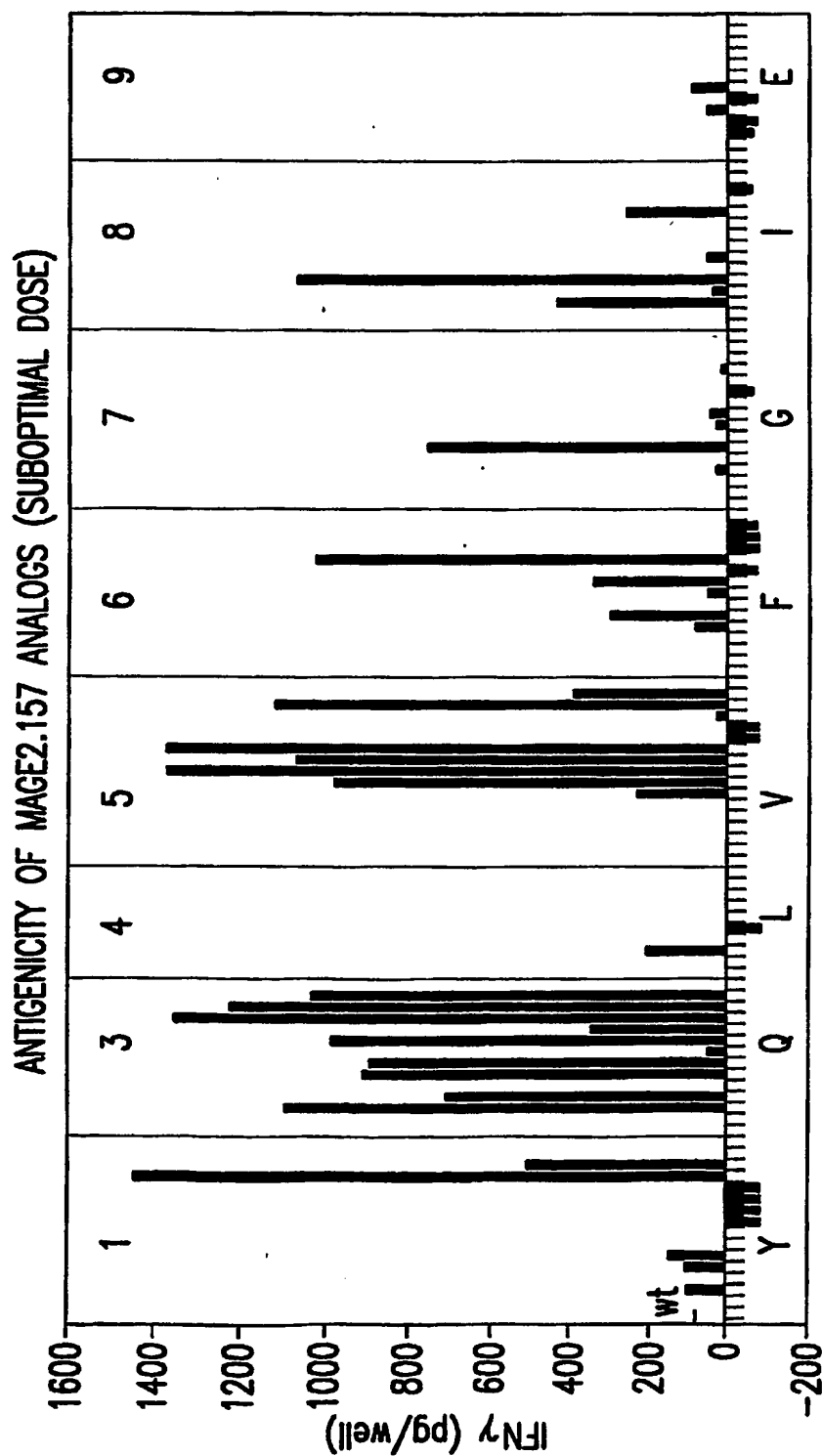


FIG.6

10/24

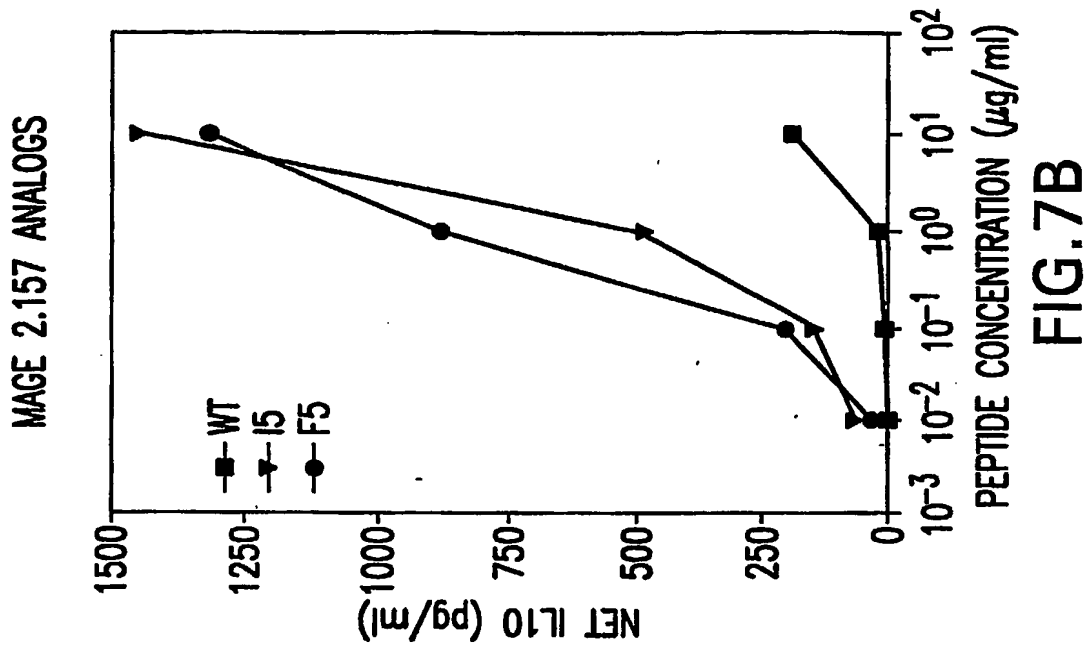


FIG.7B

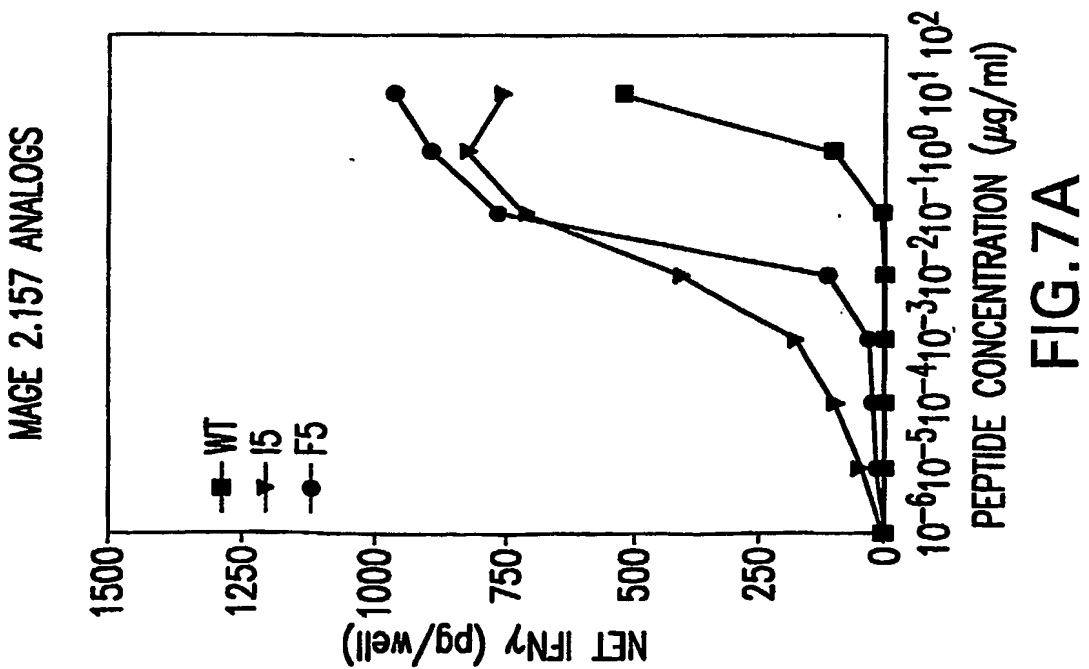


FIG.7A

11/24

□ NO PEPTIDE
■ + PEPTIDE
▨ ENDOG. PEP.-
▩ ENDOG. PEP.+

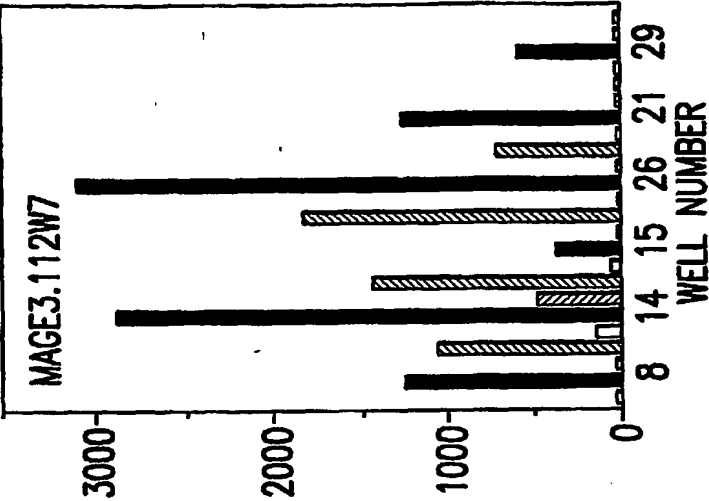


FIG.8C

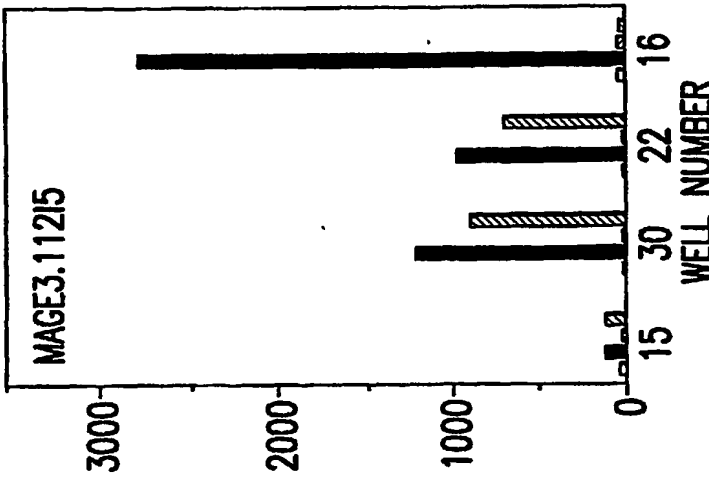


FIG.8B

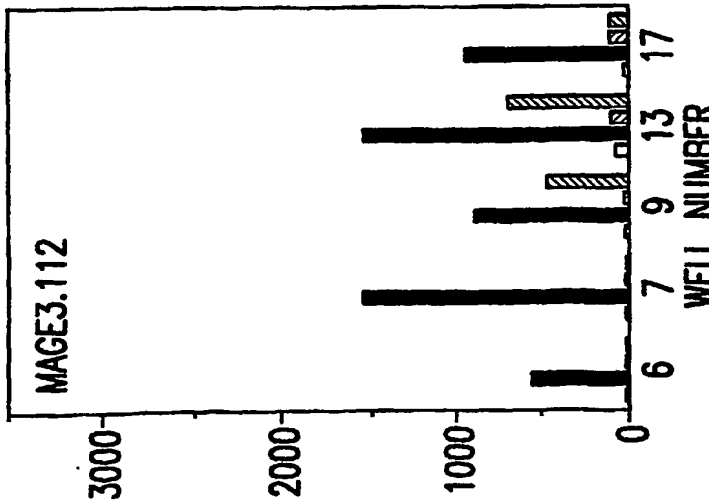
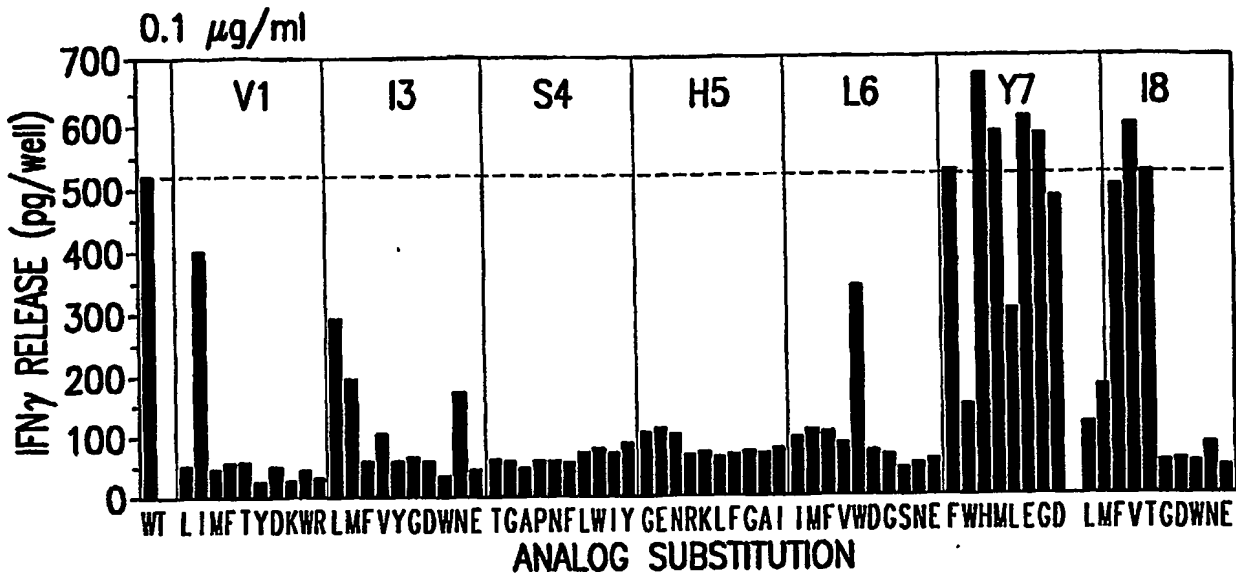


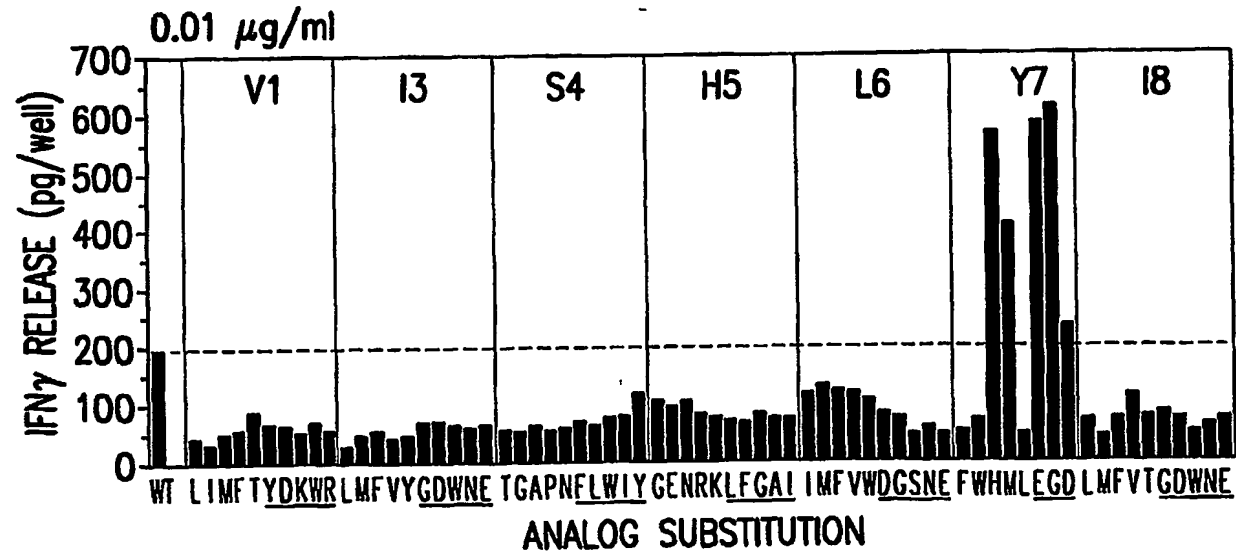
FIG.8A

12/24



SCREENING OF SINGLE AMINO ACID-SUBSTITUTED ANALOGS OF THE B7 SUPERFAMILY EPI TOPE, MAGE2.170, FOR HETEROCLITIC ACTIVITY.

FIG.9A



SCREENING OF SINGLE AMINO ACID-SUBSTITUTED ANALOGS OF THE B7 SUPERFAMILY EPI TOPE, MAGE2.170, FOR HETEROCLITIC ACTIVITY.

FIG.9B

13/24

POTENCY OF HETEROCLITIC ANALOGS OF THE MAGE2.170 EPTIPE.

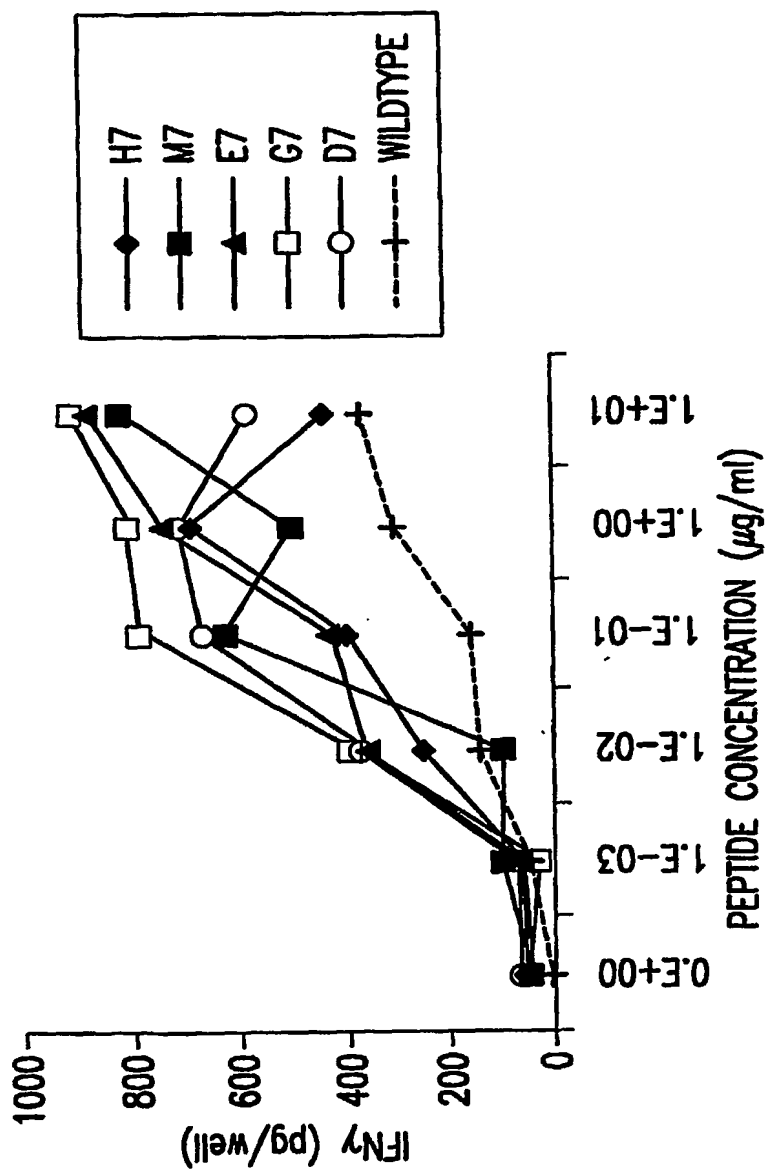


FIG.10

14/24

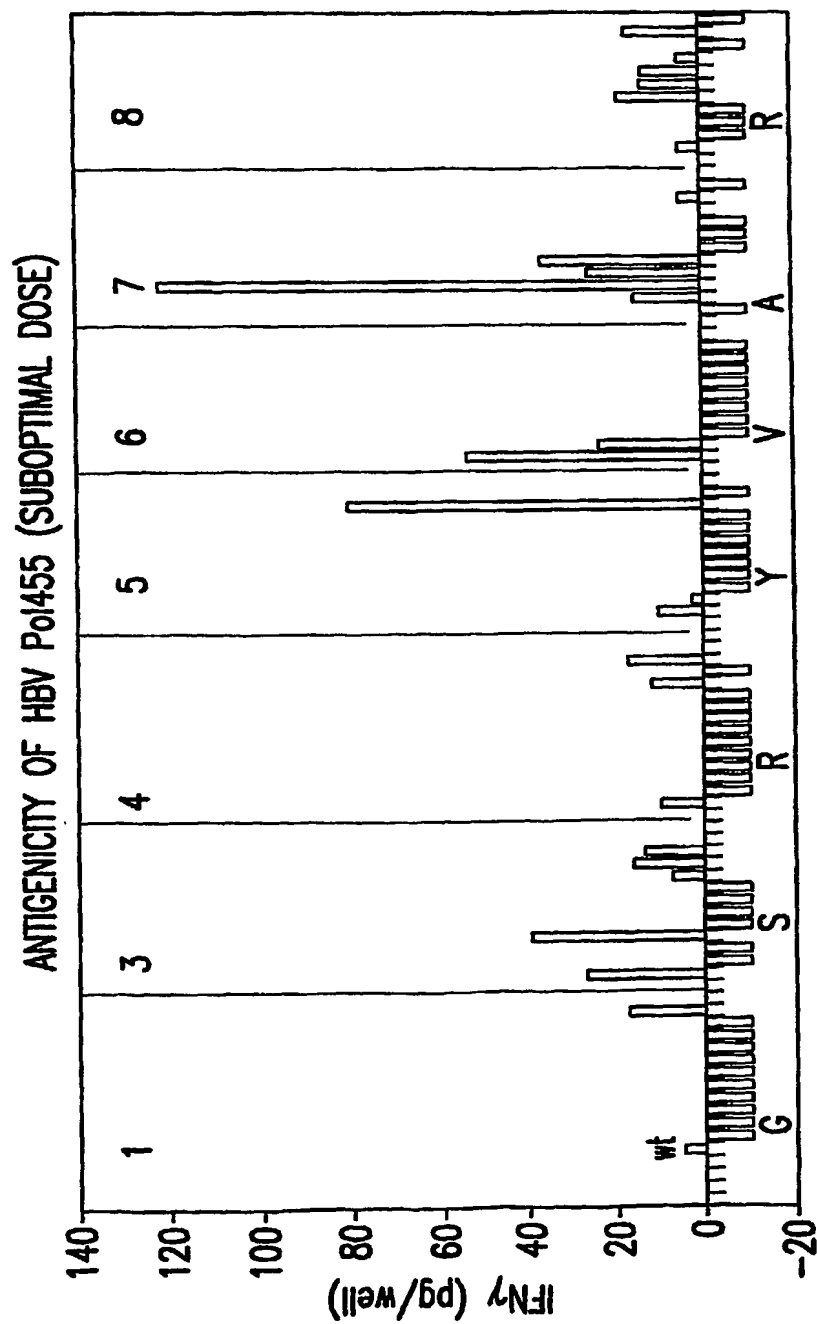
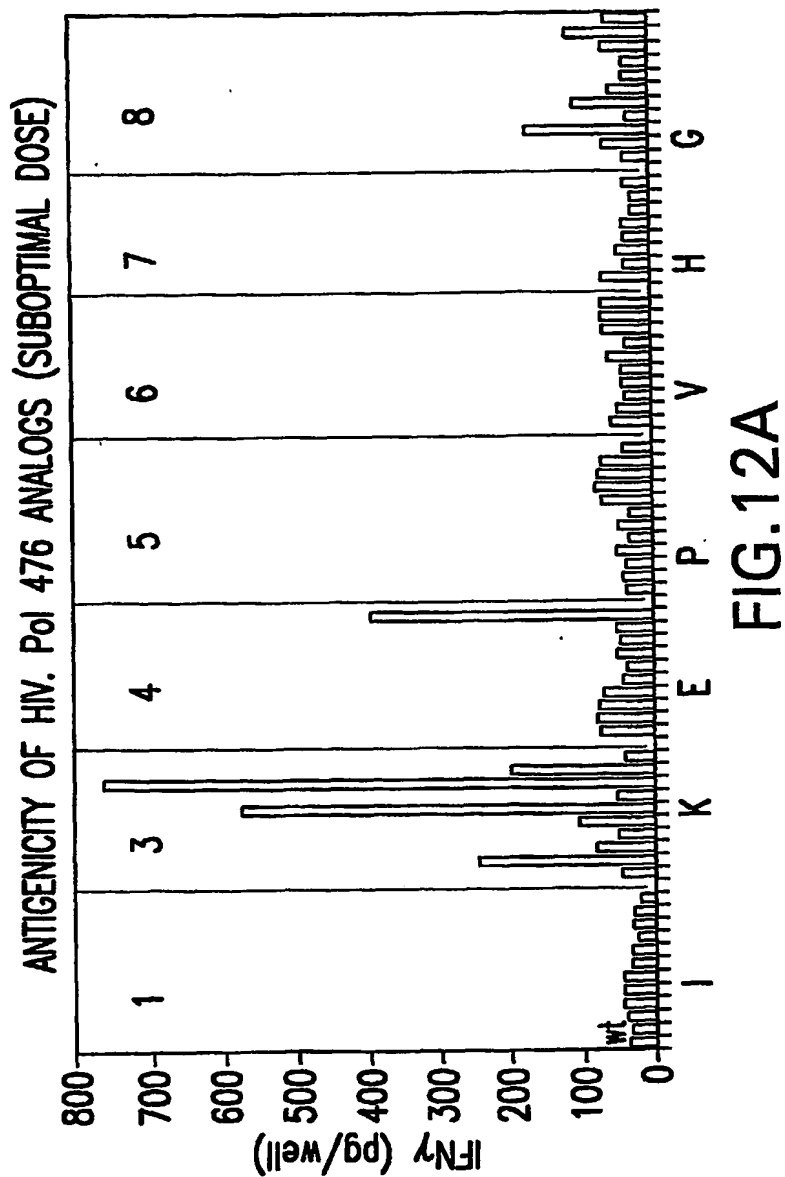
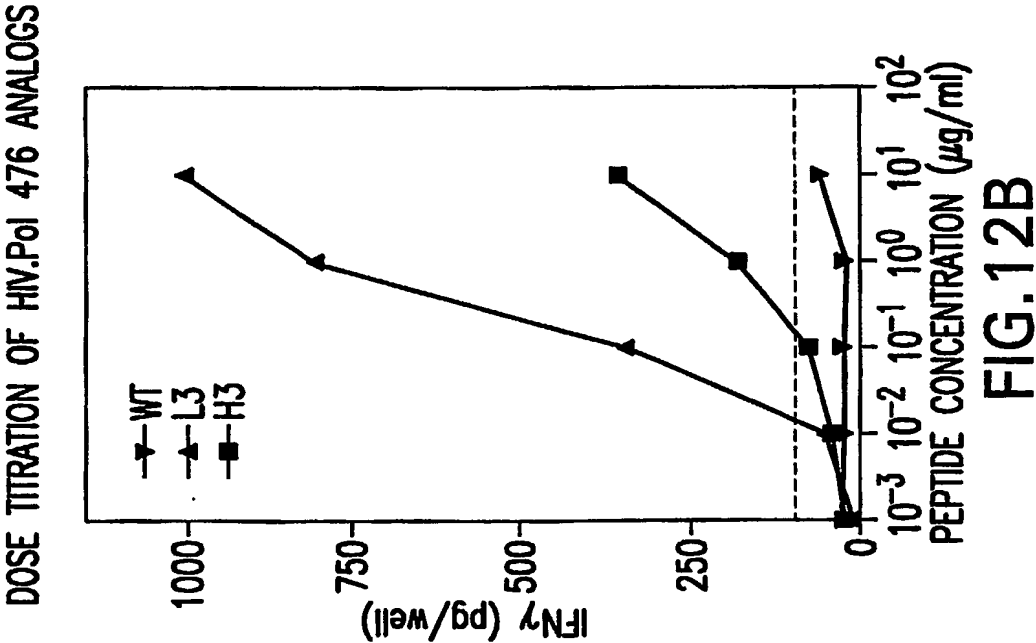


FIG.11

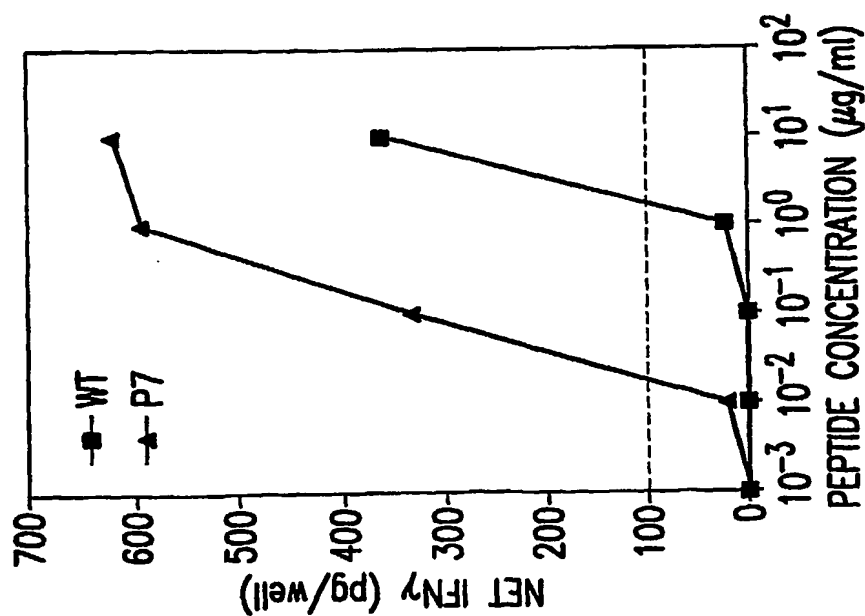
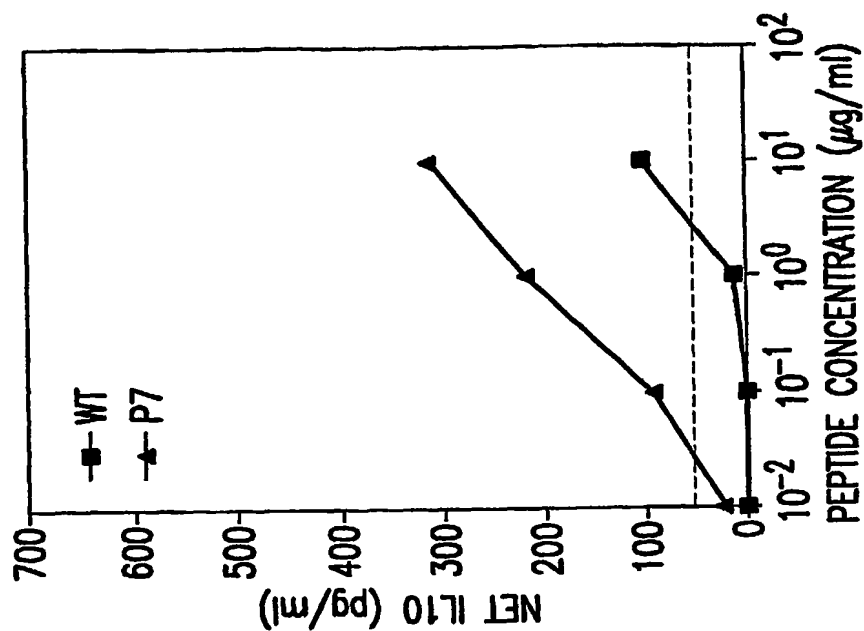
15/24



16/24



17/24



18/24

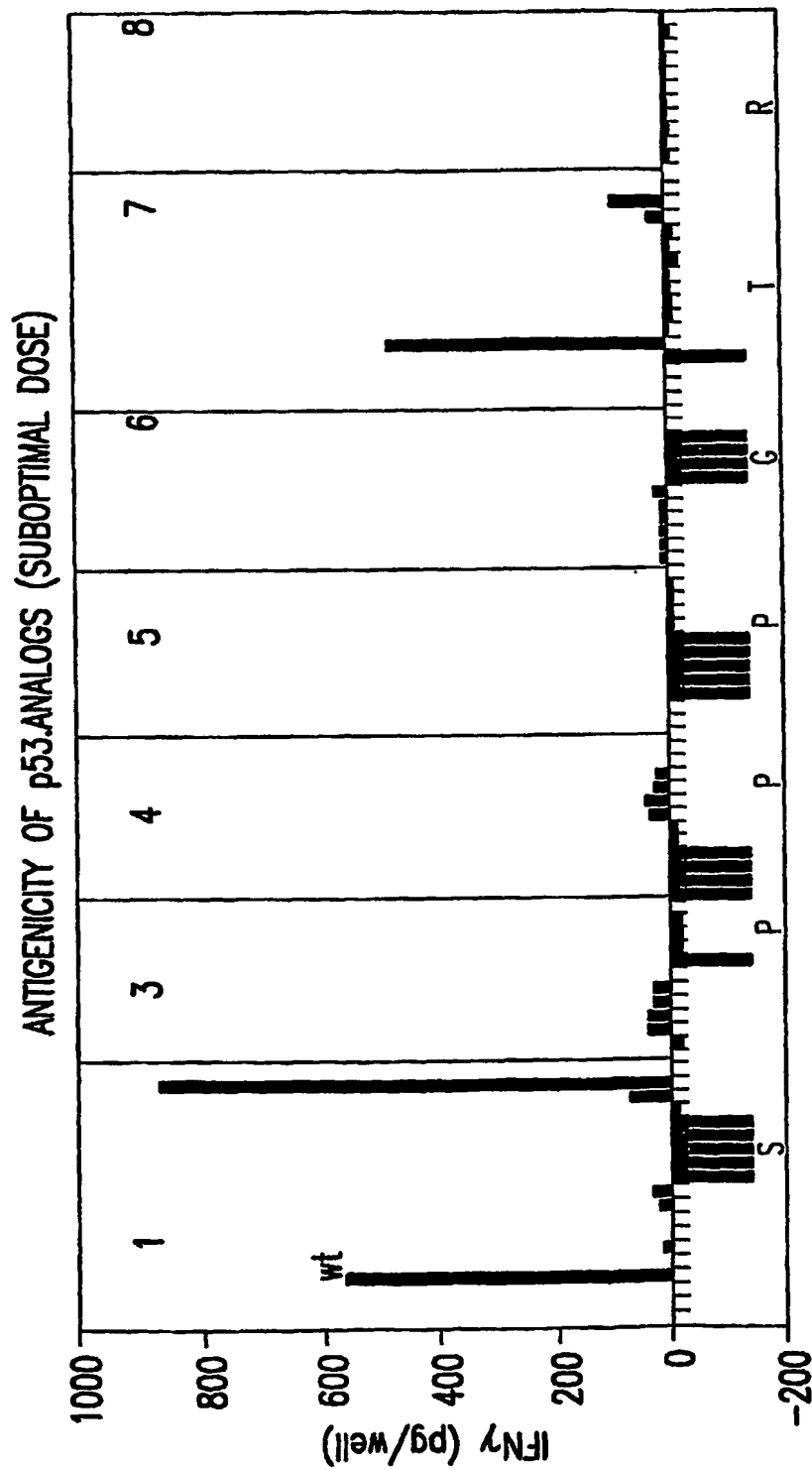


FIG.14

19/24

LYMPHOKINE PROFILE OF p53.149.M2 ANALOGS

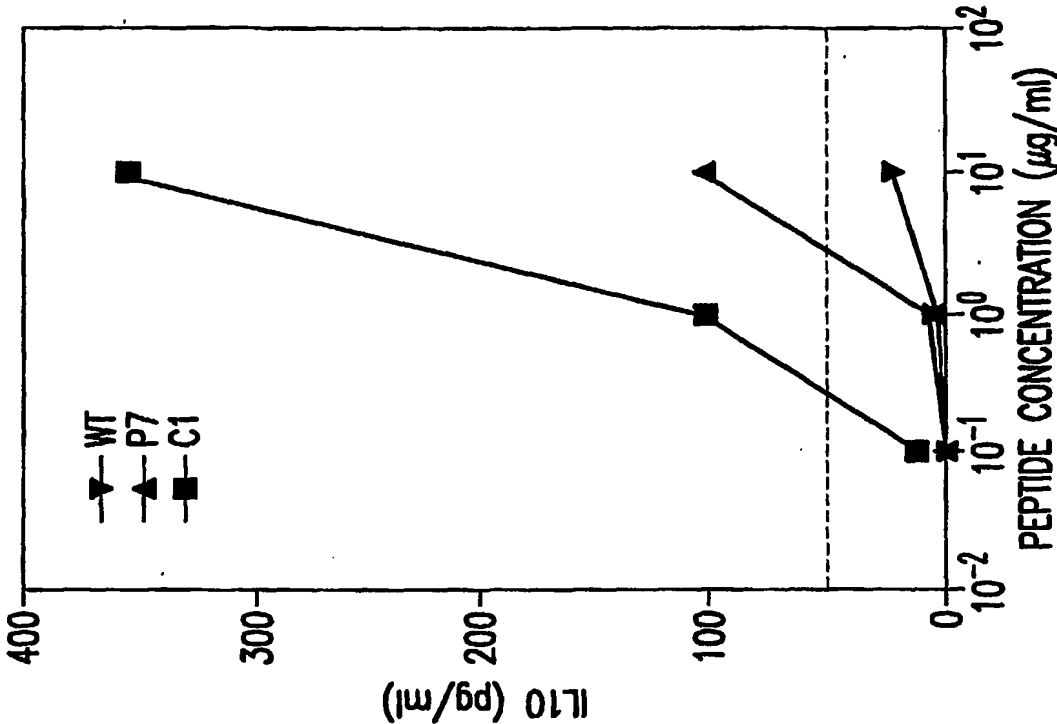


FIG.15B

LYMPHOKINE PROFILE OF p53.149.M2 ANALOGS

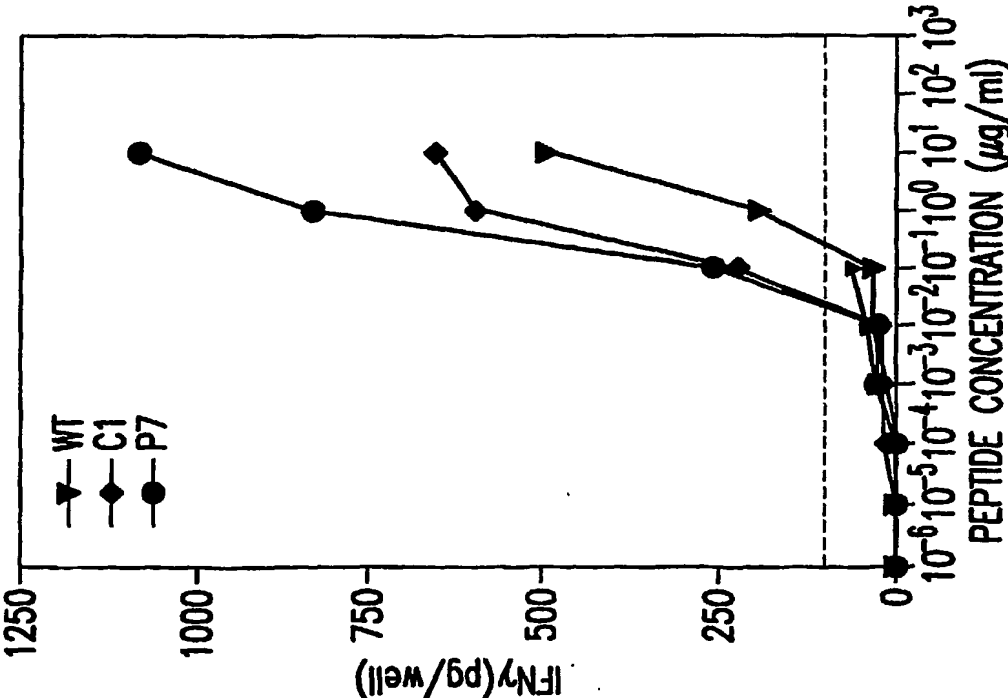
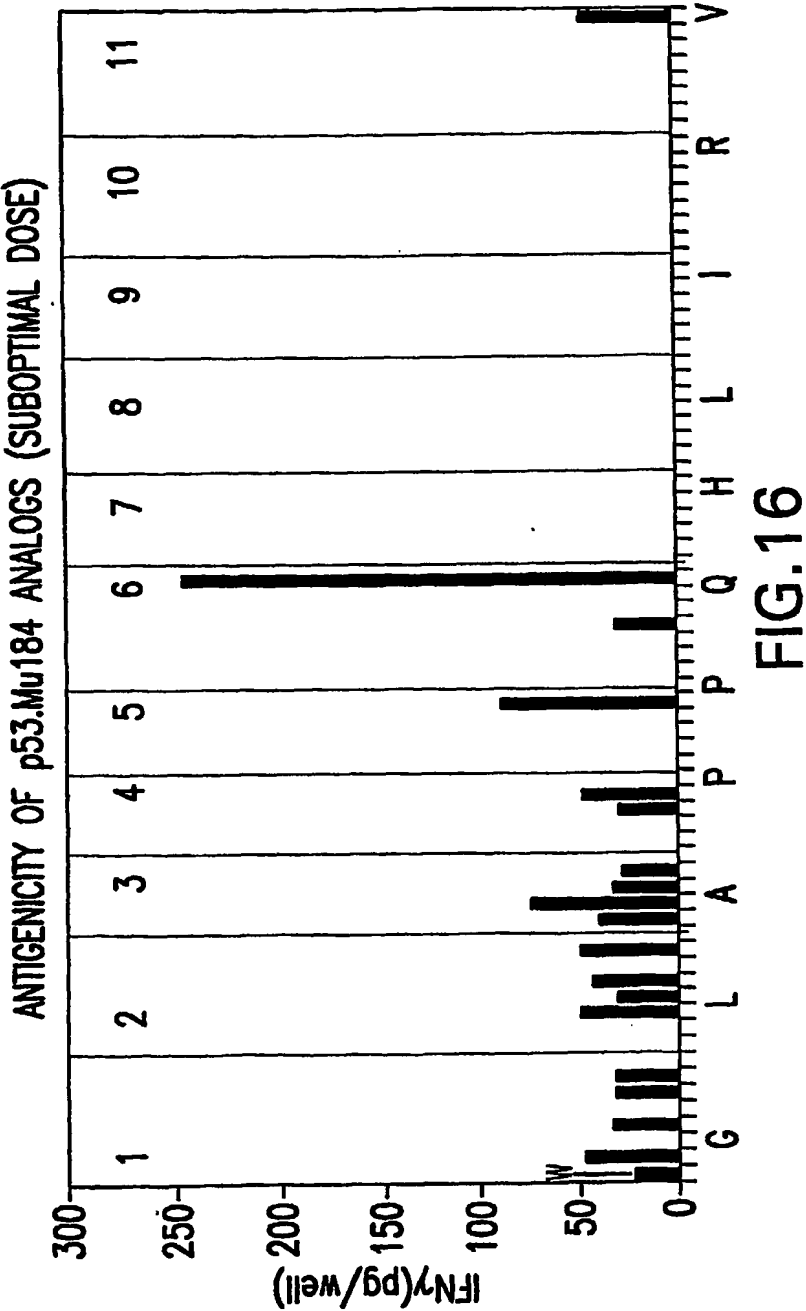


FIG.15A



21/24

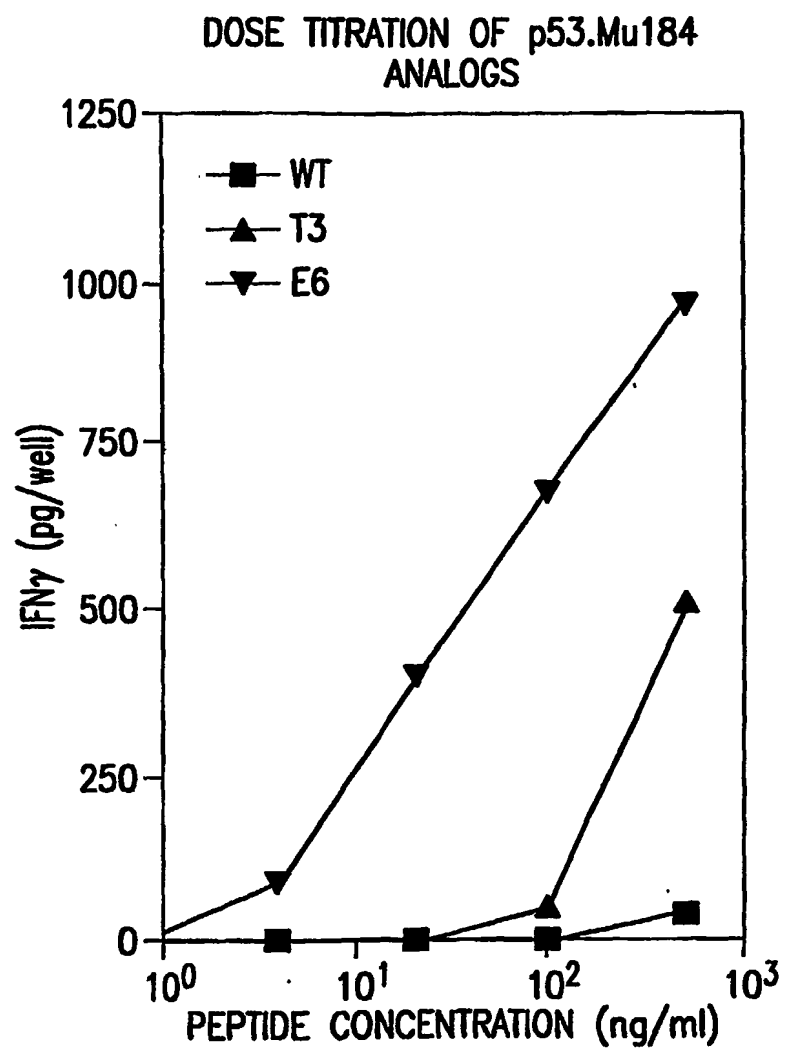


FIG.17

22/24

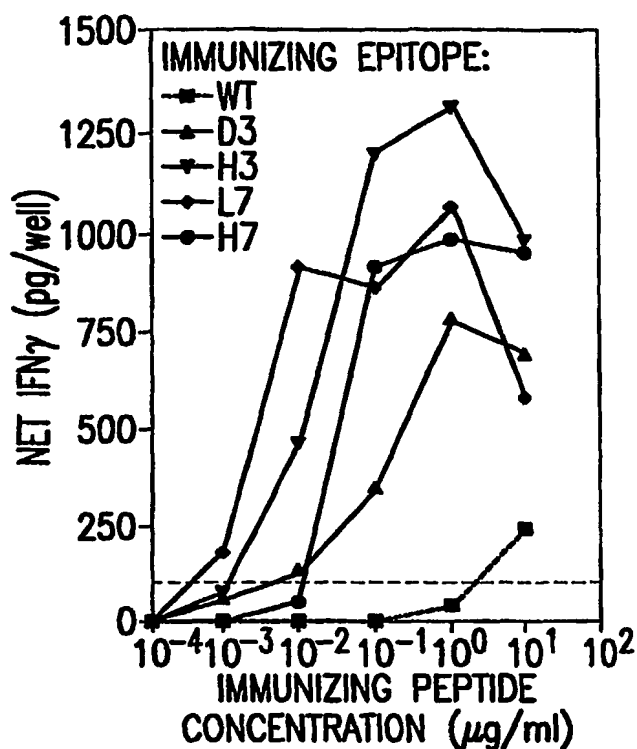


FIG. 18A

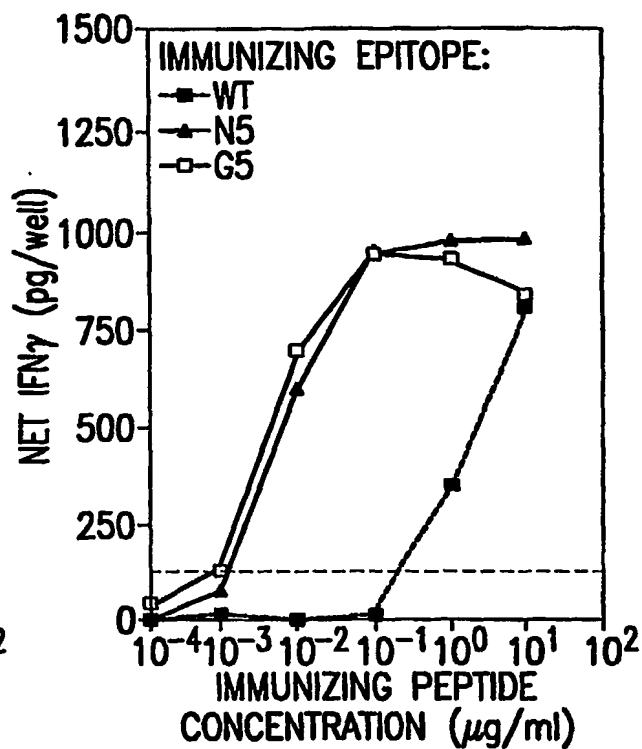


FIG. 18B

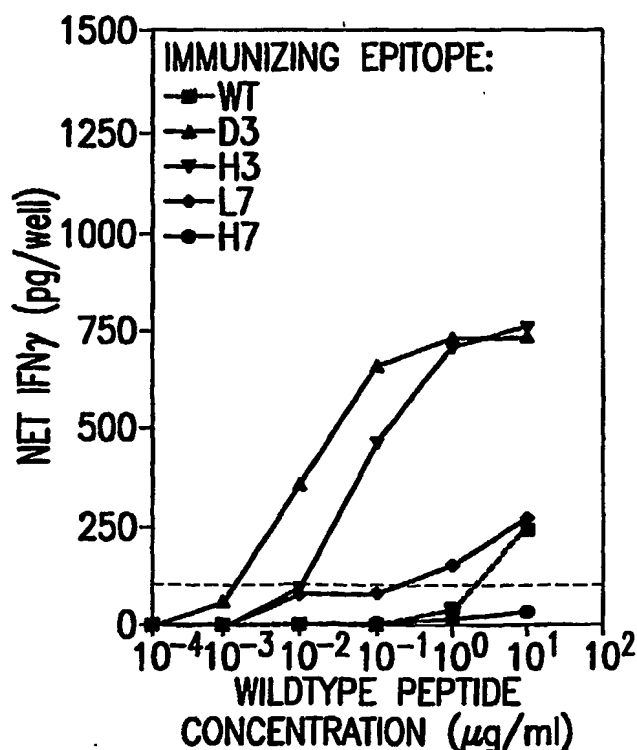


FIG. 18C

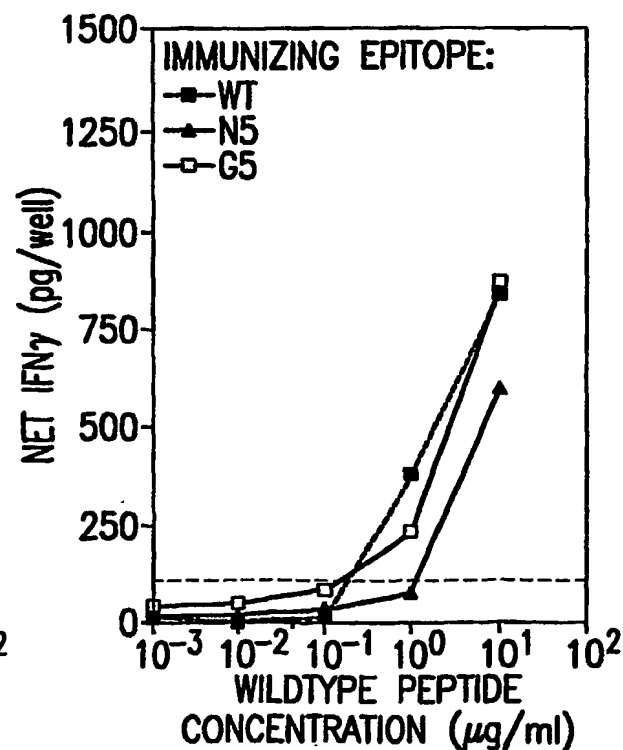
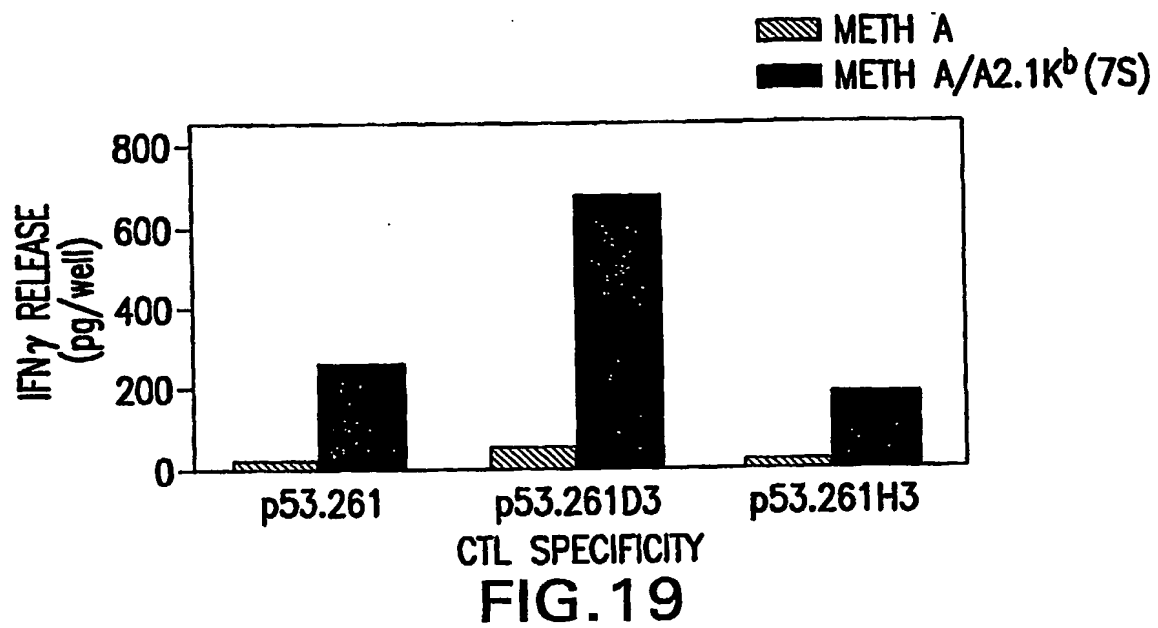


FIG. 18D

23/24



24/24

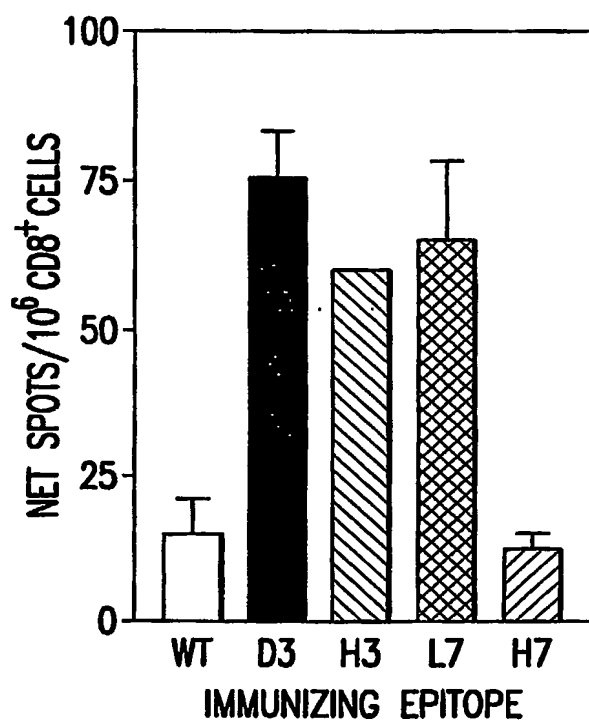


FIG. 20